REMARKS UNDER 37 CFR § 1.111

Formal Matters

Claims 1-23 are pending after entry of the amendments set forth herein, of which Claims 5-8 and 13-19 are withdrawn.

Claims 1-23 were examined. Claims 1-4, 9-12, and 20-23 were rejected.

Claims 2 and 20 have been amended. Support for these amendments is found in the claims as originally filed, as well as in the specification at, for example: Claim 2: paragraph 90, page 20; and Claim 20: paragraph 93, bridging pages 20 to 21; and paragraph 84, bridging pages 17 to 18.

Applicants respectfully request reconsideration of the application in view of the amendments and remarks made herein.

No new matter has been added.

Rejections and objections of Office Action dated August 26, 2003

The Applicants acknowledge with gratitude the Examiner's indication that the objections and rejections under 35 U.S.C. § 112, first paragraph, and 35 U.S.C. § 112, second paragraph, as set forth in the Office Action dated August 26, 2003 have been withdrawn.

Rejection under 35 U.S.C. §102

Claims 1-4 and 9-12 have been rejected under 35 U.S.C.§ 102(b) as being anticipated by Gether et al., EMBO Journal 16:6737-6747, 1997 (*hereinafter* "Gether et al."). In view of the remarks put forth below, this rejection is respectfully traversed as applied and as it may be applied to the pending claims.

The claimed invention is directed to a method of identifying a ligand for a G protein-coupled receptor (GPCR). The method involves contacting a GPCR that has a conformationally sensitive detetctable probe with a candidate agent and detecting a change in the detectable signal in the presence of the candidate agent as compared to the absence of the candidate agent. The currently pending claims recite that the GPCR have a conformationally sensitive detectable

probe "positioned on or within a conformationally sensitive third intracellular domain of the GPCR **with the proviso that the probe is not positioned in a transmembrane domain**."

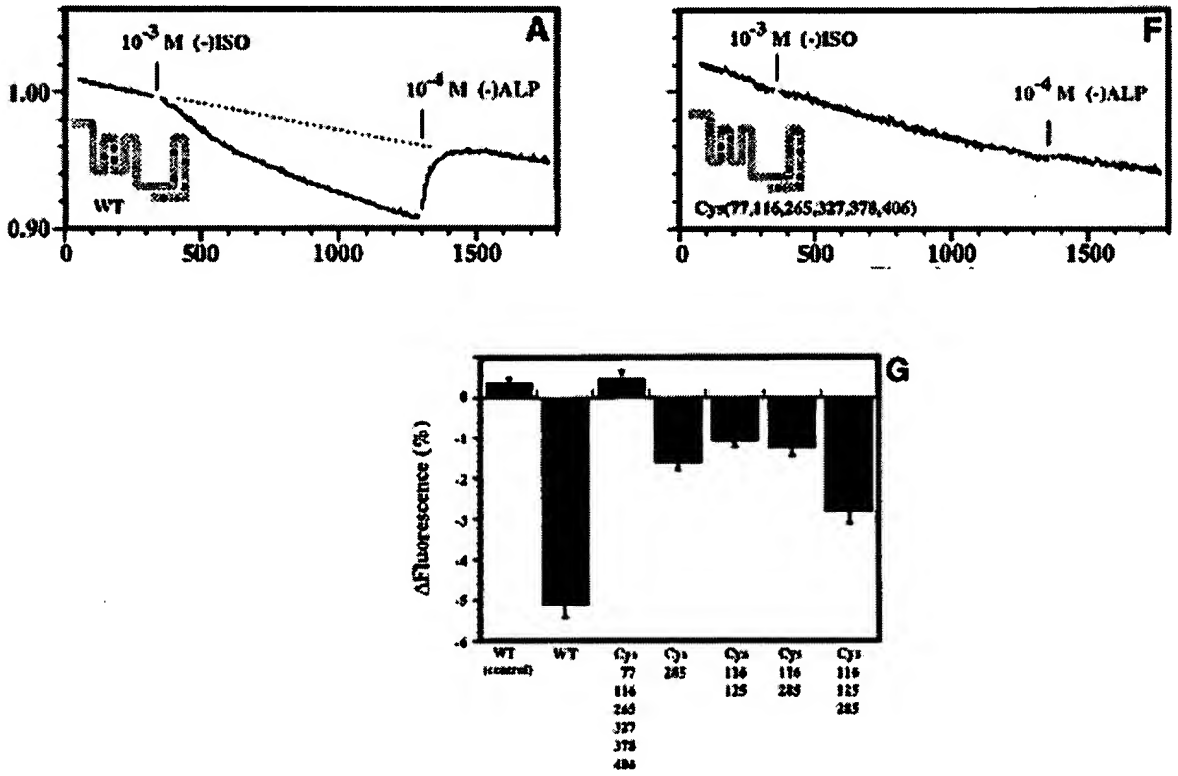
A GPCR having, for example, a detectable probe (in the form of a detectably labeled cysteine) within the third intracellular domain, without a detectable probe (e.g., labeled cysteine) within the transmembrane domain, can be generated by, for example, use of a polar fluorophore which can not access, and thus does not label, cysteine residues in the GPCR transmembrane region (see, e.g., specification on page 33, paragraph 132).

In contrast to the presently claimed invention, Gether discloses a series of labeled mutant GPCRs that were produced using the detectable label IANBD (a fluorophore capable of labeling cysteine residues in an apolar environment), which resulted in detectable labeling of cysteines at positions within the third intracellular domain **as well as positions within the transmembrane domain**. Accordingly, as noted in the response to the Office Action filed on January 26, 2004, Gether et al., does not disclose a GPCR that is labeled with a conformationally detectable probe on the conformationally sensitive third intracellular domain of the GPCR, **without such a probe being also positioned in a transmembrane domain of the receptor** (page 16).

For example, the labeled mutant-GPCR disclosed in Gether et al., (Table 1, last line) and noted in the Office Action (Page 3, last paragraph), includes a detectable label at position 265, which is in the third intracellular domain. However, the mutant GPCR also includes detectable label at positions 77, 116, and 237, which are all located in the transmembrane domain. Therefore, the labeled mutant-GPCR of Gether et al. is not the GPCR of Claim 1.

Moreover, the labeled mutant-GPCR of Gether et al. noted in the Office Action did not produce a signal change in response to the full agonist isoproterenol (see Gether et al. Figures 2A, 2F, and 2G, reproduced below for the Examiner's convenience). The data of Figure 2 is presented as a percent change in fluorescence (demarcated as the dark solid line) in response to the full agonist isoproterenol for the wild type GPCR (Fig. 2A) and the labeled mutant GPCR (Fig. 2F). Fluorescence in the presence of the agonist is compared to that of an

extrapolated baseline of fluorescence in the absence of agonist (demarcated as the dotted line) (see description of Fig. 2 on page 6740). As illustrated in Figure 2F, no change in fluorescence was observed following addition of the agonist to the mutant GPCR Cys(77, 116, 265, 327, 378, 406). The dotted line demarcating the extrapolated baseline is not visible because it essentially overlays the dark solid line. From comparison of the extrapolated baseline of Figure 2A to the actual response line of Figure 2F, it is evident that the labeled mutant-GPCR of Figure 2F did not respond to agonist. This is also reflected in the data as presented in Figure 2G, which shows the change in fluorescence with the labeled mutant-GPCR of Figure 2F (third column in Fig. 2G) is comparable to a lack of response observed with the wild-type control to which no agonist was added (first column in Fig. 2G).



This analysis is supported by the description of these results in Gether et al.:

> Analysis of the mutants revealed that agonist-induced changes in fluorescence are observed only in receptors in which ^{285}Cys or

> ^{125}Cys are present (Figure 2). A mutant lacking only these two cysteines (Cys 77, 116, 265, 327, 378, 406) **showed no response to agonist binding (Figure 2F)**.

(see first full paragraph, first column, page 6740) (emphasis added).

Accordingly, since Gether et al. fails to teach each and every element as set forth in the claims, the cited reference fails to anticipate the claimed invention. Moreover, Gether et al., also fails to teach or suggest labeling of the GPCR on or within the third intracellular domain while not labeling on or within the transmembrane domain. In fact, Gether et al., teaches away from labeling a GPCR in such a manner so as to avoid labeling of transmembrane residues because the reference hypothesizes that the more important residues for detecting a conformational change are those present in the transmembrane domain (e.g., residues 125 and 285).

In view of the above, the Applicants respectfully request that the rejection of claims 1-4 and 9-12 under 35 U.S.C. §102(b) be withdrawn.

Rejection under 35 U.S.C. §112, second paragraph

Claim 2

Claim 2 has been rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention. In particular, the Office Action states that Claim 2 is indefinite because it recites "agonist activity." Without conceding to the correctness of the rejection, Claim 2 has been amended to recite "a conformational change in the GPCR **in the presence** of the candidate agent." Support for the amendment can be found in the claims as originally filed, as well as in the specification at, for example page 20, paragraph 90. In view of the amendment to Claim 2, withdrawal of this objection is respectfully requested.

Claims 20-23

Claims 20-23 has been rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention. In particular, the Office Action states that Claims 20 is indefinite because it is unclear how the ligand for a specific GPCR among a plurality of GPCRs is identified.

In the sprit of expediting prosecution and without conceding to the correctness of the rejection, Claim 20 has been amended to recite "**wherein the GPCRs are provided on an array at assigned coordinates**," and "detection of a change in the detectable signal **at a coordinate on the array** in the presence of the candidate agent as compared to the absence of the candidate agent indicates the candidate agent is a ligand for the GPCR **at the coordinate on the array**." Support for the amendment can be found in the claims as originally filed, as well as in the specification at, for example paragraph 93, bridging pages 20 to 21, and paragraph 84, bridging pages 17 to 18. In view of the amendment to Claim 20, withdrawal of this objection is respectfully requested.

Conclusion

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number STAN-213.

Respectfully submitted,
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Date: July 1, 2004

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